Prenatal Diagnosis of Cytomegalovirus Infection

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Prenatal Diagnosis of Cytomegalovirus Infection

Cytomegalovirus (CMV) infection at any stage during pregnancy can result in fetal damage or death. Congenital infections acquired during the first trimester are associated with more severe symptoms, sequelae, and abnormalities. CMV IgG and IgM serology plays a valuable role in identifying pregnancies at risk for prenatal CMV infection.

By Hans Ijpeelaar, MSc, MEd
Cytomegalovirus (CMV) is a common virus that infects most people at some point during their lives. It is a member of the herpes virus family. Most children and adults who are infected with CMV do not develop symptoms. Although the virus is not highly communicable, it can be spread from person to person by direct contact. The virus is shed in the urine, saliva, semen, and to a lesser extent in other body fluids. Transmission can also occur from an infected mother to her fetus or newborn and by blood transfusion and organ transplants.

**Maternal Cytomegalovirus Infection Prevalence Varies by Region**

Infection prevalence in North America and Europe is about 50 percent, while in some parts of Japan, South America, and Africa, prevalence is close to 100 percent. Since CMV is transmitted via body fluids, it has been suggested that these dramatic differences in infection rates reflect the varying levels of hygiene and close social contact in these regions. Fetal CMV infection is the leading cause of mental retardation after Down Syndrome. Worldwide, CMV is a common viral cause of congenital abnormalities. In the U.S., it is the most common source of congenital infection, central nervous system (CNS) damage, and sensorineural hearing loss. Long-term CNS sequelae include motor and visual deficits, and seizures.

Although CMV infection can pose a serious risk to a developing fetus, mothers who become infected during the first 16 weeks of the pregnancy are at a higher risk for transmission to the fetus than those infected later in pregnancy, and these early infections carry a higher risk for CNS sequelae, especially sensorineural hearing loss.

In rare cases, a severe, generalized infection of the neonate may occur: cytomegalic inclusion disease. This condition is associated with jaundice, purpura, petechiae, hepatosplenomegaly, thrombocytopenia, hemolytic anemia, microcephaly, intra-cerebral calcifications, and chorioretinitis. The affected organs have enlarged atypical cells that are characterized by owl’s-eye-shaped inclusions. The prognosis is poor.

**Congenital Infection**

Congenital infection results from vertical transmission, that is, direct transmission of the virus from infected mother to fetus or neonate. Vertical transmission may occur in utero via the placenta or in the birth canal during labor and delivery or in the postnatal period through breast milk. Infections acquired via breast milk are generally asymptomatic; however, studies in Germany and Canada suggest that some low-birth weight and preterm infants that are breast-fed may be at risk for the symptoms and sequelae associated with CMV infection.

In utero, vertical transmission results from the spread of the virus to the placenta. The placenta then serves as a reservoir in which CMV replicates before being transmitted to the fetus. Once transmitted to the fetus, it initially infects endothelial cells and, later, other target tissues. Possible outcomes of placental infection range from no fetal infection to fetal death from infection. Moreover,
reactivated infections, and reinfection with a different CMV strain. In latent infections there is no production of the virus: the virus remains sequestered in mononuclear leukocytes and in the cells of organs like the kidney and the heart. The virus can begin replicating at any time, thereby causing a reactivated infection.

In pregnancy, the distinction is useful because primary infection has a higher rate of transmission to the fetus. Stagno et al. found that in pregnancies with primary maternal infection, 30 to 40 percent of the fetuses had congenital infection, whereas in immune mothers (recurrent infection), fewer than one percent were infected (Figure 1). More neonates with congenital CMV are symptomatic at birth in primary maternal infection than in recurrent infection (Figure 2a): symptom rates for primary infection range from 10 to 18 percent and for recurrent infection from 0 to 1 percent. Primary maternal infection is also associated with an increased risk of sequelae and more severe sequelae. In one study, 25 percent of infants born to mothers with primary infection and 8 percent of infants born to mothers with recurrent infection had sequelae associated with CMV infection (Figure 2b). While recurrent maternal infection is somewhat protective against sequelae, these infants are still at risk.

### Key Clinical Considerations
- Infection at any stage during pregnancy can result in fetal damage or death; however, congenital infections acquired during the first trimester are associated with more severe symptoms, sequelae, and abnormalities.
- Either recurrent infection or primary infection of the mother can result in congenital infection.
- Many congenitally infected babies do not develop abnormalities.
- Symptomatic and asymptomatic congenitally infected babies are at risk for serious long-term sequelae, including sensorineural hearing loss and mental retardation.

### Prenatal Diagnosis of CMV Infection
Diagnosis of prenatal CMV infection is a process. Generally, maternal infection is diagnosed first, followed by fetal diagnosis. Congenital infection is diagnosed when CMV is detected either in amniotic fluid, fetal tissue, fetal blood, or in neonatal urine samples within the first two weeks of life. Diverse tests for detecting CMV infection are well described in the literature. CMV IgG and IgM serology are valuable for identifying pregnancies at risk for prenatal CMV infection. A number of methods currently in use have proven to be useful adjuncts to CMV IgG and IgM serology. They include serum IgG avidity, glycoprotein B, PCR, Western blots from mother-baby pairs, and ultrasound. Avidity and PCR methods are widely used in Europe and may become more widely available in the U.S. While ultrasound is limited in its ability to detect CMV infections, it is useful for evaluating the presence of structural abnormalities that are associated with fetal CMV infection. Lipitz, et al. found abnormal ultrasound in 21 to 42 percent of fetal infections. Abnormal ultrasound was associated with worse neonatal outcomes than normal ultrasound. Ultrasound, therefore, is useful as a follow-up test in cases of documented fetal infection because it can provide valuable prognostic information about neonatal outcome.

### Symptomatic versus Asymptomatic Infection at Birth—Implications for the infant and child
The presence of symptoms at birth is associated with a much higher risk of sequelae. Even though most infected infants are asymptomatic at birth, studies suggest some of them eventually develop serious sequelae, including deafness and mental retardation. For example, the rates of hearing loss among children with symptomatic CMV infection at birth range from 10 to 65 percent, and from 0 to 23 percent in those asymptomatic at birth.
Maternal Diagnosis via Serology: Primary or Recurrent Infection

Ideally, the first step in the diagnosis of prenatal CMV infection is the diagnosis of maternal CMV infection. The best documentation of a primary infection is seroconversion, which is demonstrated by de novo detection of CMV-specific antibodies in a pregnancy that was previously negative. CMV IgM detection is a sensitive indicator of recent or ongoing infection; high levels of IgM are usually linked to primary infection. IgM levels alone, however, are not sufficient to diagnose primary CMV infection because CMV IgM can also be detected during recurrent infection and primary Epstein-Barr virus (EBV) infection (via cross-reactive antigens). A mother’s positive CMV IgM result does not mean that the fetus will be infected; it requires further testing to determine whether there is a primary or recurrent CMV infection or an EBV infection. Landini and Lazzarotto have proposed a diagnostic protocol to identify pregnancies at high risk for primary CMV infection (Figure 3).16

Conclusions

Although children and adults infected with CMV are rarely symptomatic, CMV infection can pose a serious risk to a developing fetus. It is a leading cause of congenital abnormalities worldwide. While maternal screening for CMV has not been universally implemented, significant advances have been made to improve screening techniques to accurately diagnose CMV infection in pregnant women.

• CMV IgM is a useful first-line test for identifying pregnancies at risk for congenital CMV infection.
• Maternal testing must determine whether CMV infection is primary or recurrent because primary maternal infection presents a greater risk for congenital infection and long-term sequelae.
• Primary maternal CMV infection documented via CMV IgG or IgM serology requires further testing to determine if the virus was transmitted to the fetus.

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References


Spotlight
CMV: The Virus Nobody Talks About

By Lisa Saunders

The moment Elizabeth was born in 1989, I felt a stab of fear. My immediate thought was, “Her head looks so small—so deformed.”

The neonatologist declared, “Your daughter has profound microcephaly—her brain is very small with calcium deposits throughout. If she lives, she will never roll over, sit up, or feed herself.” He concluded that Elizabeth’s birth defects were caused by congenital cytomegalovirus (CMV)—a virus that may have no symptoms for the mother, known as a “silent virus,” or that may present itself with mild to severe flu-like symptoms to a mother during pregnancy.

How and why did I catch this virus that I had barely heard of? The CMV literature stated that women who care for young children are at a higher risk for catching it, as preschoolers are the majority of carriers. The virus is spread through bodily fluids such as saliva and urine. Pregnant women need to be careful not to kiss young children on or around the mouth or share food or towels with them. Hands must be washed after diaper changes, wiping runny noses, etc. Why hadn’t my OB/GYN warned me about this?

While I was pregnant with Elizabeth, I not only had a toddler of my own, but also ran a licensed daycare center in my home. I felt sick at what my ignorance had done to my little girl. In milder cases, children with congenital CMV may lose hearing or struggle with learning disabilities later in life. But Elizabeth’s case was not a mild one.

Today, I am committed to preventing others from going through what Elizabeth did. Although congenital CMV causes more disabilities in children than Down syndrome (Figure 1) and can be prevented through careful handling of saliva and other bodily fluids, very few women have heard of CMV (Figure 2). Not all OB/GYNs warn women of childbearing age about the infection and how to avoid it. A May 2007 survey conducted by the American College of Obstetricians and Gynecologists (ACOG) found that fewer than half (44%) of OB/GYNs surveyed reported counseling their patients about preventing CMV infection.


Lisa Saunders is a CMV Foundation Parent Advocate and the founder of the website, www.authorlisasaunders.com and has written a memoir, Anything But a Dog! The perfect pet for a girl with congenital CMV. She lives in Mystic, Connecticut.
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